PCT/EP00/06171

PA NT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 15 March 2001 (15.03.01)	
International application No. PCT/EP00/06171	**Applicant's or agent's file reference** SCB/52246002
International filing date (day/month/year) 30 June 2000 (30.06.00)	**Priority date** (day/month/year) 02 July 1999 (02.07.99)
Applicant GEERTS, Hugo, Alfons, Gabriel et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

24 January 2001 (24.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
SCB/52246002		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 06171	30/06/2000	02/07/1999
Applicant		
JANSSEN PHARMACEUTICA N.V.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   DOUBLE TRANSGENIC ANIMALS AS MODELS FOR NEURODEGENERATIVE DISEASE

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 14

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 44-48

Present claims 44 to 48 relate to a compound, a composition comprising it and methods using thereof, defined by reference to a desirable characteristic, namely being obtainable by a method of screening using a transgenic animal as described in claim 43.
The claims cover all compounds having this characteristic, all compositions comprising them and all methods using thereof, whereas the application provides no support within the meaning of Article 6 PCT and no disclosure within the meaning of Article 5 PCTs. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has not been carried out for those parts of the claims which appear to be not clear, not supported and disclosed.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

There is provided transgenic animals comprising:1.a nucleic acid vector a) sequence encoding a human Tau protein; (b) a sequence capable of directing expression of said human Tau protein in the nervous system of a non-human animal; and (c) a targeting sequence which facilitates integration of said vector into the genome of said animal so as to prevent expression of equivalent Tau protein; a nucleic acid vector comprising: (a) a nucleic acid sequence encoding a human protein capable of modulating human Tau protein; (b) a sequence capable of directing expression of said protein in the nervous system of said animal; and (c) a targeting sequence capable of facilitating integration of said vector into the genome of said animal optionally at a position corresponding to a sequence in said animal encoding an equivalent of said human protein.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06171

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/00 A01K67/027 C07K14/47 C12N5/10 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 05466 A (INST OF PSYCHIATRY ;ANDERTON BRIAN HENRY (GB); MILLER CHRISTOPHER) 23 February 1995 (1995-02-23) page 4, line 1 - line 12 page 15, line 30 -page 16, line 6	40,43
Y	page 12, line 25; claims 12-15,20,30-38,45-49	1-51
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2001	04/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Chambonnet, F

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	GUO Q, SEBASTIAN L, SOPHER BL, MILLER MW, WARE CB, MARTIN GM, MATTSON MP.: "Increased vulnerability of hippocampal neurons from presenilin-1 mutant knock-in mice to amyloid beta-peptide toxicity: central roles of superoxide production and caspase activation." JOURNAL OF NEUROCHEMISTRY, vol. 72, no. 3, March 1999 (1999-03), pages 1019-1029, XP001020319 page 1020, column 1, paragraph 3 -column 2, paragraph 3 ---	1-51
Y	MICHEL GOEDERT & MASATO HASEGAWA.: "The Tauopathies Toward an Experimental Animal Model" AMERICAN JOURNAL OF PATHOLOGY, vol. 154, no. 1, January 1999 (1999-01), pages 1-6, XP002923749 page 3, column 2, paragraph 2 ---	1-11, 30-33
Y	GÖTZ, J. ET AL.: "Somatodendritic localization and hyperphosphorylation of tau protein in transgenic mice expressing the longest human brain tau isoform" EMBO JOURNAL, vol. 14, no. 7, 3 April 1995 (1995-04-03) - 1304, page 1313 XP002175363 EYNSHAM, OXFORD GB cited in the application the whole document ---	1-9, 30-33
Y	BRION J-P ET AL: "TRANSGENIC EXPRESSION OF THE SHORTEST HUMAN TAU AFFECTS ITS COMPARTMENTALIZATION AND ITS PHOSPHORYLATION AS IN THE PRETANGLE STAGE OF ALZHEIMER'S DISEASE" AMERICAN JOURNAL OF PATHOLOGY, PHILADELPHIA, PA, US, vol. 154, no. 1, January 1999 (1999-01), pages 255-270, XP000965124 ISSN: 0002-9440 the whole document ---	1-6, 30-33
A	KÜHN ET AL: "Advances in gene targeting methods" CURRENT OPINION IN IMMUNOLOGY, CURRENT BIOLOGY LTD. LONDON, GB, vol. 9, 1997, pages 183-188, XP002133099 ISSN: 0952-7915 the whole document ---	1-40

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2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SAUER BRIAN: "Inducible gene targeting in mice using the Cre/lox system." METHODS, vol. 14, April 1998 (1998-04), pages 381-392, XP001019712 figures 2-4 ---	10,11,38
Y	BROWNLEES J ET AL: "TAU PHOSPHORYLATION IN TRANSGENIC MICE EXPRESSING GLYCOGEN SYNTHASE KINASE-3BETA TRANSGENES" NEUROREPORT,RAPID COMMUNICATIONS OF OXFORD, OXFORD,GB, vol. 8, no. 15, 20 October 1997 (1997-10-20), pages 3251-3255, XP000974561 ISSN: 0959-4965 cited in the application the whole document ---	12
Y	HARADA A. ET AL.: "Altered microtubule organization in small-calibre axons of mice lacking tau protein" NATURE., vol. 369, no. 6480, 9 June 1994 (1994-06-09), pages 488-491, XP002175364 MACMILLAN JOURNALS LTD. LONDON., GB ISSN: 0028-0836 the whole document ---	30-33
P,Y	SPITTAELS K ET AL: "PROMINENT AXONOPATHY IN THE BRAIN AND SPINAL CORD OF TRANSGENIC MICE OVEREXPRESSING FOUR-REPEAT HUMAN TAU PROTEIN" AMERICAN JOURNAL OF PATHOLOGY,PHILADELPHIA, PA,US, vol. 155, no. 6, December 1999 (1999-12), pages 2153-2165, XP000974569 ISSN: 0002-9440 the whole document ---	1-19
T	SPITTAELS K, ET AL.: "Glycogen synthase kinase-3beta phosphorylates protein tau and rescues the axonopathy in the central nervous system of human four-repeat tau transgenic mice" J BIOL CHEM. , vol. 275, no. 52, 29 December 2000 (2000-12-29), pages 41340-41349, XP002175365 the whole document ---	12

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	DAWSON, H.N. ET AL.: "Tau distribution in a human tau gene transgenic/mouse tau knock out model" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 25, no. 1-2, October 1999 (1999-10), page 790 XP001020341 abstract & 29th Annual Meeting of the Society for Neuroscience, Miami Beach, Florida, USA October 23-28 1999 ---	30
T	DAWSON, H.N. ETAL.: "Inhibition of neuronal maturation in primary hippocampal neurons from tau deficient mice" JOURNAL OF CELLULAR BIOLOGY, vol. 114, no. pt 6, March 2001 (2001-03), pages 1179-1187, XP001020383 the whole document -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/06171

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9505466 A	23-02-1995	EP 0716700 A	19-06-1996
		GB 2295395 A,B	29-05-1996
		US 5994084 A	30-11-1999

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SCB/52246002		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06171	30/06/2000	02/07/1999
International Patent Classification (IPC) or national classification and IPC C12N15/00		
Applicant JANSSEN PHARMACEUTICA N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/01/2001	19.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herrmann, K Telephone No. +49 89 2399 2670

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06171

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-55 as originally filed

Claims, No.:

1-50 as received on 24/10/2001 with letter of 23/10/2001

Drawings, sheets:

1/21-21/21 as originally filed

Sequence listing part of the description, pages:

1-3, filed with the letter of 20.10.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☒ the claims, Nos.: 51

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 43-47.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 43-47 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-42, 48-50
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-42, 48-50
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-42, 48-50
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Citations

The documents mentioned in this International Preliminary Examination Report (IPER) are numbered as in the International Search Report (ISR) dated 04.09.01, i.e. **D1** and **D13** correspond to the first and the last document of the search report, respectively.

Re ITEM I (Basis of the opinion)

1 Amended claims 1-50 filed with letter of 23.10.01 can be regarded as meeting the requirements of Art. 34(2)(b) PCT.

2 Sequence listing pages 1-3 (9 sequences) filed with the letter of 20.10.00 do not form part of the application (Rule 13ter.1(f) PCT).

Re ITEM II (Priority)

D10 and **D12** indicated in the search report as P-documents are not to be regarded as state of the art according to Rule 64(1)(b) PCT, as the date of priority claimed (02.07.99) can be allowed for the relevant parts of the present application.

Re ITEM III (Non-establishment of opinion)

The International Preliminary Examining Authority (IPEA) agrees with the objection put forward by the International Searching Authority (ISA) as to insufficiency of disclosure and support concerning the subject-matter of claims 43-47 (Art. 5 and 6 PCT). Present claims 43-47 relate to a product defined by reference to a desirable characteristic or property, namely that it is obtainable by the method of claim 42 (product-by-process). The compounds as such are not sufficiently defined by their mode of action. Consequently, claims 43-47 have not been searched and examined because "a compound which modulates human kinase mediated phosphorylation of human Tau protein" is neither disclosed nor supported within the terms of Art. 5 and 6 PCT, respectively.

R ITEM V (Nov lty, inv ntiv step, industrial applicability)

1 **Novelty (Art. 33(2) PCT)**

The subject-matter of claims 1-42, 48-50 has not been made available to the public by any of the available prior art documents and can therefore be regarded as novel.

2 **Inventive step (Art. 33(3) PCT)**

The subject-matter of claims 1-42, 48-50 cannot be derived from the available prior art in an obvious manner and therefore complies with the requirements of Art. 33(3) PCT.

The subject-matter of originally filed claim 8, which is regarded as novel and inventive by this authority, has been incorporated in independent claims 1 and 11. The subject-matter of originally filed claim 34, which is regarded as novel and inventive by this authority, has been incorporated in independent claims 29. The transgenic non-human animal according to independent claim 38 can also be regarded as novel and inventive.

3 **Industrial applicability (Art. 33(4) PCT)**

Claims 1-42 and 48-50 meet the criteria as set forth by Art. 33(4) PCT.

Re ITEM VII (Certain defects in the international application)

The present application contains such a high number of independent claims that the application as a whole lacks conciseness (Rule 6.1(a) PCT). For example, independent claims 23, 29, 33 and 48 are all directed to "A method of making a transgenic non-human animal". The same objection applies *mutatis mutandis* independent claims 1 and 11 ("A nucleic acid knockin-knockout vector") and to independent claims 37, 38 and 50 ("A transgenic non-human animal").

R ITEM VIII (C rtain observations on the international application)

1 It is clear from the description (p. 25-48) that the features concerning the human Tau protein (as in claim 5), the modulation of human Tau (as in claim 13), the sequence capable of directing expression of said human Tau 40 isoform and said GSK-3β kinsase (as in claims 7 and 16) and the "targeting sequence" (as in claims 10 and 18) are essential to the performance of the invention; i.e. the alleged technical problem of providing an animal model of neurodegenerative diseases is only solved when all the above mentioned conditions are met. The solution to the problem is a double transgenic mouse overexpressing human GSK-3β and human protein tau. Since the independent do not contain all the essential technical features of the alleged invention they do not meet the requirements of Rule 6.3 PCT (also cf. PCT Guidelines III-4.4).

2 Claim 19 also encompasses an isolated human embryonic stem cell and thus does not exclude transgenic human beings. E.g. claims 23(b) and 29(b) are not restricted to female non-human animals. Thus, it is not excluded the embryo from step (a) may be introduced into a female human being. Further, the subject-matter of claims 20-41 and 48-50 (transgenic animals and methods for the production thereof) may not be allowable in certain PCT member states.

3 In claim 29 the word "exhibiting" is used instead of "comprising" (Art. 6 PCT) (cf. orgininal claim 34: "comprising a region of homology...")

CLAIMS

1. A nucleic acid knockin-knockout vector comprising:

(a) a nucleic acid sequence encoding a human Tau protein;

(b) a sequence capable of directing expression of said human Tau protein in the nervous system of a non-human animal; and

(c) a targeting sequence wherein said targeting sequence comprises a nucleotide sequence exhibiting a sufficient degree of homology with said sequence encoding said equivalent Tau protein in said animal or flanking sequences thereof, to facilitate integration of said vector into the genome of said animal by homologous recombination, so as to prevent expression of equivalent Tau protein or a related or equivalent protein from said animal in favour of said human Tau protein.

2. A vector according to claim 1 further comprising a sequence encoding a reporter molecule.

3. A vector according to claim 2 wherein said reporter molecule comprises the hygromycin. Pgk-hyg marker gene sequence.

4. A vector according to any of claims 1 to 3 wherein said sequence encoding human Tau is a cDNA sequence.

5. A vector according to claim 4 wherein said cDNA sequence encodes a Tau 40 isoform.

6. A vector according to any preceding claim wherein said sequence capable of directing expression of said

human Tau protein is a mouse promoter.

7. A vector according to claim 6 wherein said mouse promoter is a Thy-1 promoter.

8. A vector according to any preceding claim wherein said targeting sequence comprises a NcoI restriction site corresponding to the unique NcoI restriction site of exon1 of the Tau sequence in the mouse wild type genome.

9. A vector according to any of claims 1 to 8 further comprising two loxP sites flanking either of the sequences of step (a) and (b).

10. A vector according to any of claims 1 to 8 further comprising a stop sequence capable of preventing expression of said human Tau protein and which sequence is flanked by two loxP sites capable of undergoing reciprocal conservative DNA recombination in the presence of Cre recombinase with the resulting excision of said stop sequence.

11. A nucleic acid knockin-knockout vector comprising:

(a) a nucleic acid sequence encoding a human protein capable of modulating human Tau protein;

(b) a sequence capable of directing expression of said protein in the nervous system of a non-human animal; and

(c) a targeting sequence capable of facilitating integration of said vector into the genome of said animal at a position corresponding to a sequence in said animal encoding an equivalent of said human protein so as to prevent expression of said equivalent

sequence in favour of said human protein capable of modulating human Tau protein, wherein said targeting sequence comprises a nucleotide sequence exhibiting a sufficient degree of homology with said sequence encoding said equivalent of said human protein capable of modulating Tau or flanking sequences thereof.

12. A vector according to claim 11 wherein said human protein is capable of phosphorylating a human Tau protein.

13. A vector according to claim 11 or 12 wherein said human protein is GSK-3β kinase.

14. A vector according to any of claims 11 to 13 wherein said nucleic acid sequence in step a) is a cDNA sequence.

15. A vector according to any of claims 11 to 14 wherein said sequence capable of directing expression of said protein capable of modulating human Tau protein is a mouse promoter.

16. A vector according to claim 15 wherein said promoter is a Thy-1 promoter.

17. A vector according to any of claims 11 to 15 further comprising two loxP sites flanking either of the sequences of step (a) and (b).

18. A vector according to any of claims 11 to 16 further comprising a stop sequence capable of preventing expression of said protein capable of modulating human Tau protein, and which stop sequence

is flanked by two loxP sites capable of undergoing reciprocal conservative DNA recombination in the presence of Cre recombinase with the resulting excision of the stop sequence.

19. An isolated host cell transformed, transfected or injected with a vector according to any one of the preceding claims.

20. A host cell according to claim 19 wherein the cell is a non-human animal cell.

21. A host cell according to claim 20 wherein said non-human animal cell is a non-human mammalian embryo cell.

22. A host cell according to claim 21 wherein said cell is an embryonic stem cell.

23. A method of making a transgenic non-human animal comprising the steps of:

(a) introducing into an embryo cell of said animal one or more of a nucleic acid vector according to any of claims 1 to 18;

(b) introducing the embryo from step (a) into a female animal;

(c) sustaining the female in step (b) until such time as the embryo has sufficiently developed and is borne from the female; and

(d) sustaining the transgenic animal.

24. A method according to claim 23 wherein said vector is introduced firstly into a non-human embryonic stem cell which is subsequently introduced into a blastocyst of said animal.

25. A method according to claim 24 wherein both of

the vectors encoding said human Tau and said protein capable of modulating human Tau according to claims 1 to 10 and 11 to 18 respectively are introduced into said stem cell.

26. A method according to any of claims 23 to 25 wherein said non-human animal is a mammal.

27. A method according to claim 26 wherein said mammal is a mouse.

28. A method according to claim 23 or 24, comprising the step of introducing a vector according to any of claims 1 to 10 into a first animal and a vector according to any of claims 11 to 18 into a second animal, crossing said first and second animals and selecting among the progeny those that express both said human Tau and said protein capable of modulating human Tau protein.

29. A method of making a transgenic non-human animal, which expresses a human Tau protein comprising the steps of:

(a) introducing sequentially or simultaneously into an embryo cell of said animal a first nucleic acid vector comprising a transgene capable of expressing said human Tau protein in the nervous system of said animal and a second nucleic acid vector comprising a sequence of nucleotides exhibiting a region of homology with a sequence encoding an equivalent Tau protein in said animal or with a region flanking or adjacent said sequence so as to facilitate integration of said vector into the genome of said animal by homologous recombination and which upon integration into the genome of said animal

is capable of preventing expression of endogenous Tau protein from said animal;

(b) introducing the embryo from step (a) into a female animal,

(c) sustaining the female in step (b) until such time as the embryo has sufficiently developed and is borne from the female; and

(d) sustaining the transgenic animal.

30. A method according to claim 29 wherein each of said first and second nucleic acid vectors are introduced in the same embryo cell.

31. A method according to claim 29 or 30 wherein said transgenic non-human animal is a mammal.

32. A method according to claim 31 wherein said mammal is a mouse.

33. A method of generating a transgenic non-human animal which is a model for Alzheimers disease or related neurodegenerative disorders, comprising the steps of crossing a first transgenic non-human animal comprising a vector according to any of claims 1 to 10 in its genome with a second transgenic non-human animal comprising a vector according to any of claims 11 to 18 in its genome, selecting among the progeny those that express both human Tau protein and said protein capable of modulating human Tau protein.

34. A method according to claim 33 wherein said nucleic acid vector in said first transgenic animal comprises a vector according to claim 9 or 10.

35. A method according to claim 34 wherein said second transgenic animal comprises a vector according to any of claims 11 to 18.

36. A method according to claim 34 which further comprises introducing into said second animal a vector comprising a transgene encoding Cre recombinase.

37. A transgenic non-human animal obtainable according to the methods of any of claims 23 to 36.

38. A transgenic knockin-knockout non-human animal that is a model for neurodegenerative disorders, comprising:

(a) an introduced DNA sequence encoding and capable of expressing heterologous Tau protein in the nervous system of the animal so as to prevent expression of the equivalent Tau protein in said animal or a related or equivalent protein in said animal in favour of said heterologous Tau protein; and

(b) a DNA sequence encoding and capable of expressing a protein capable directly or indirectly of modulating said heterologous Tau protein.

39. A transgenic non-human animal according to claim 38 wherein said sequence in step (a) comprises a vector according to any of claims 1 to 10.

40. A transgenic non-human animal according to claim 38 wherein said sequence according to step (b) comprises a vector according to any of claims 11 to 18.

41. A transgenic non-human animal according to claim 40 wherein said sequence according to step (b) is a kinase.

42. A method of identifying a compound which

modulates human kinase mediated phosphorylation of human Tau protein which method comprises administering a test compound to a non-human animal according to claim 41 expressing both said human Tau protein and said human kinase and monitoring the phosphorylation profile of said Tau protein compared to one of said transgenic animals which has not been administered with the compound.

43. A compound obtainable according to the method of claim 42.

44. A pharmaceutical composition comprising a compound according to claim 43 together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

45. Use of a compound according to claim 43 in the manufacture of a medicament for the treatment of neurodegenerative disorders.

46. Use according to claim 45, wherein said neurodegenerative disorders comprise any of FTDP-17 (Fronto-temporal dementia associated with Parkinson's disease), Cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy, Pick's disease, Dementia Pugilistica, Dementia with tangles only, dementia with tangles and calcification, Down syndrome, Myotonic dystrophy, Niemann Pick's disease type C, Parkinsonism-dementia complex of Guam, Postencephalic Parkinsonism, Prion diseases with tangles, subacute sclerosing panencephalitis.

47. A method of treating neurodegenerative disorders mediated by phosphorylation of human Tau protein comprising administering to a patient a compound as defined in claim 43 or a composition according to

claim 44.

48. A method of generating a transgenic non-human animal which is a model for Alzheimers disease or related neurodegenerative disorders, comprising the steps of crossing a first transgenic non-human animal comprising a vector having, i) a nucleic acid sequence encoding a human Tau protein, ii) a sequence capable of directing expression of said human Tau protein in the nervous system of said animal and iii) a targeting sequence which comprises a nucleotide sequence exhibiting a sufficient degree of homology with equivalent Tau protein in said animal or flanking sequences thereof, which facilitates integration of said vector into the genome of said animal by homologous recombination; with a second transgenic non-human animal comprising a vector according to claim 11, selecting among the progeny those that express both human Tau protein and said protein capable of modulating Tau protein.

49. A method according to claim 48 wherein said vector in said first and/or said second transgenic non-human animal comprises a stop sequence capable of preventing expression of said human Tau protein or said protein capable of modulating Tau protein which sequence is flanked by two loxP sites capable of undergoing reciprocal conservative DNA recombination with the resulting excision of said stop sequence.

50. A transgenic non-human animal obtainable according to the method of claim 48 or 49.

PATENT COOPERATION TREATY

by fax and post

Miss Baldock
Gislata
DATE 21/11/01

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BALDOCK, Sharon Claire
BOULT WADE TENNANT
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15 NOV 2001
13.40
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22 NOV 2001
Patent departme

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	19.11.2001
Applicant's or agent's file reference: SCB/52246002	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06171	30/06/2000	02/07/1999

Applicant: JANSSEN PHARMACEUTICA N.V.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Cleere, C Tel.+49 89 2399-7713

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SCB/52246002		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06171	30/06/2000	02/07/1999
International Patent Classification (IPC) or national classification and IPC C12N15/00		
Applicant JANSSEN PHARMACEUTICA N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/01/2001	19.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herrmann, K Telephone No. +49 89 2399 2670

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06171

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-55 as originally filed

Claims, No.:

1-50 as received on 24/10/2001 with letter of 23/10/2001

Drawings, sheets:

1/21-21/21 as originally filed

Sequence listing part of the description, pages:

1-3, filed with the letter of 20.10.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/EP00/06171

- ☐ the description, pages:
- ☒ the claims, Nos.: 51
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
   see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 43-47.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06171

☒ the claims, or said claims Nos. 43-47 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-42, 48-50
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-42, 48-50
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-42, 48-50
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Citations

The documents mentioned in this International Preliminary Examination Report (IPER) are numbered as in the International Search Report (ISR) dated 04.09.01, i.e. **D1** and **D13** correspond to the first and the last document of the search report, respectively.

Re ITEM I (Basis of the opinion)

1 Amended claims 1-50 filed with letter of 23.10.01 can be regarded as meeting the requirements of Art. 34(2)(b) PCT.

2 Sequence listing pages 1-3 (9 sequences) filed with the letter of 20.10.00 do not form part of the application (Rule 13ter.1(f) PCT).

Re ITEM II (Priority)

D10 and **D12** indicated in the search report as P-documents are not to be regarded as state of the art according to Rule 64(1)(b) PCT, as the date of priority claimed (02.07.99) can be allowed for the relevant parts of the present application.

Re ITEM III (Non-establishment of opinion)

The International Preliminary Examining Authority (IPEA) agrees with the objection put forward by the International Searching Authority (ISA) as to insufficiency of disclosure and support concerning the subject-matter of claims 43-47 (Art. 5 and 6 PCT). Present claims 43-47 relate to a product defined by reference to a desirable characteristic or property, namely that it is obtainable by the method of claim 42 (product-by-process). The compounds as such are not sufficiently defined by their mode of action. Consequently, claims 43-47 have not been searched and examined because "a compound which modulates human kinase mediated phosphorylation of human Tau protein" is neither disclosed nor supported within the terms of Art. 5 and 6 PCT, respectively.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/EP00/06171

Re ITEM V (Novelty, inventive step, industrial applicability)

1 **Novelty (Art. 33(2) PCT)**

The subject-matter of claims 1-42, 48-50 has not been made available to the public by any of the available prior art documents and can therefore be regarded as novel.

2 **Inventive step (Art. 33(3) PCT)**

The subject-matter of claims 1-42, 48-50 cannot be derived from the available prior art in an obvious manner and therefore complies with the requirements of Art. 33(3) PCT.

The subject-matter of originally filed claim 8, which is regarded as novel and inventive by this authority, has been incorporated in independent claims 1 and 11. The subject-matter of originally filed claim 34, which is regarded as novel and inventive by this authority, has been incorporated in independent claims 29. The transgenic non-human animal according to independent claim 38 can also be regarded as novel and inventive.

3 **Industrial applicability (Art. 33(4) PCT)**

Claims 1-42 and 48-50 meet the criteria as set forth by Art. 33(4) PCT.

Re ITEM VII (Certain defects in the international application)

The present application contains such a high number of independent claims that the application as a whole lacks conciseness (Rule 6.1(a) PCT). For example, independent claims 23, 29, 33 and 48 are all directed to "A method of making a transgenic non-human animal". The same objection applies *mutatis mutandis* independent claims 1 and 11 ("A nucleic acid knockin-knockout vector") and to independent claims 37, 38 and 50 ("A transgenic non-human animal").

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/EP00/06171

Re ITEM VIII (Certain observations on the international application)

1 It is clear from the description (p. 25-48) that the features concerning the human Tau protein (as in claim 5), the modulation of human Tau (as in claim 13), the sequence capable of directing expression of said human Tau 40 isoform and said GSK-3β kinsase (as in claims 7 and 16) and the "targeting sequence" (as in claims 10 and 18) are essential to the performance of the invention; i.e. the alleged technical problem of providing an animal model of neurodegenerative diseases is only solved when all the above mentioned conditions are met. The solution to the problem is a double transgenic mouse overexpressing human GSK-3β and human protein tau. Since the independent do not contain all the essential technical features of the alleged invention they do not meet the requirements of Rule 6.3 PCT (also cf. PCT Guidelines III-4.4).

2 Claim 19 also encompasses an isolated human embryonic stem cell and thus does not exclude transgenic human beings. E.g. claims 23(b) and 29(b) are not restricted to female non-human animals. Thus, it is not excluded the embryo from step (a) may be introduced into a female human being. Further, the subject-matter of claims 20-41 and 48-50 (transgenic animals and methods for the production thereof) may not be allowable in certain PCT member states.

3 In claim 29 the word "exhibiting" is used instead of "comprising" (Art. 6 PCT) (cf. orgininal claim 34: "comprising a region of homology...")

CLAIMS

1. A nucleic acid knockin-knockout vector comprising:

(a) a nucleic acid sequence encoding a human Tau protein;

(b) a sequence capable of directing expression of said human Tau protein in the nervous system of a non-human animal; and

(c) a targeting sequence wherein said targeting sequence comprises a nucleotide sequence exhibiting a sufficient degree of homology with said sequence encoding said equivalent Tau protein in said animal or flanking sequences thereof, to facilitate integration of said vector into the genome of said animal by homologous recombination, so as to prevent expression of equivalent Tau protein or a related or equivalent protein from said animal in favour of said human Tau protein.

2. A vector according to claim 1 further comprising a sequence encoding a reporter molecule.

3. A vector according to claim 2 wherein said reporter molecule comprises the hygromycin Pgk-hyg marker gene sequence.

4. A vector according to any of claims 1 to 3 wherein said sequence encoding human Tau is a cDNA sequence.

5. A vector according to claim 4 wherein said cDNA sequence encodes a Tau 40 isoform.

6. A vector according to any preceding claim wherein said sequence capable of directing expression of said

human Tau protein is a mouse promoter.

7. A vector according to claim 6 wherein said mouse promoter is a Thy-1 promoter.

8. A vector according to any preceding claim wherein said targeting sequence comprises a NcoI restriction site corresponding to the unique NcoI restriction site of exon1 of the Tau sequence in the mouse wild type genome.

9. A vector according to any of claims 1 to 8 further comprising two loxP sites flanking either of the sequences of step (a) and (b).

10. A vector according to any of claims 1 to 8 further comprising a stop sequence capable of preventing expression of said human Tau protein and which sequence is flanked by two loxP sites capable of undergoing reciprocal conservative DNA recombination in the presence of Cre recombinase with the resulting excision of said stop sequence.

11. A nucleic acid knockin-knockout vector comprising:

(a) a nucleic acid sequence encoding a human protein capable of modulating human Tau protein;

(b) a sequence capable of directing expression of said protein in the nervous system of a non-human animal; and

(c) a targeting sequence capable of facilitating integration of said vector into the genome of said animal at a position corresponding to a sequence in said animal encoding an equivalent of said human protein so as to prevent expression of said equivalent

sequence in favour of said human protein capable of modulating human Tau protein, wherein said targeting sequence comprises a nucleotide sequence exhibiting a sufficient degree of homology with said sequence encoding said equivalent of said human protein capable of modulating Tau or flanking sequences thereof.

12. A vector according to claim 11 wherein said human protein is capable of phosphorylating a human Tau protein.

13. A vector according to claim 11 or 12 wherein said human protein is GSK-3β kinase.

14. A vector according to any of claims 11 to 13 wherein said nucleic acid sequence in step a) is a cDNA sequence.

15. A vector according to any of claims 11 to 14 wherein said sequence capable of directing expression of said protein capable of modulating human Tau protein is a mouse promoter.

16. A vector according to claim 15 wherein said promoter is a Thy-1 promoter.

17. A vector according to any of claims 11 to 15 further comprising two loxP sites flanking either of the sequences of step (a) and (b).

18. A vector according to any of claims 11 to 16 further comprising a stop sequence capable of preventing expression of said protein capable of modulating human Tau protein, and which stop sequence

is flanked by two loxP sites capable of undergoing reciprocal conservative DNA recombination in the presence of Cre recombinase with the resulting excision of the stop sequence.

19. An isolated host cell transformed, transfected or injected with a vector according to any one of the preceding claims.

20. A host cell according to claim 19 wherein the cell is a non-human animal cell.

21. A host cell according to claim 20 wherein said non-human animal cell is a non-human mammalian embryo cell.

22. A host cell according to claim 21 wherein said cell is an embryonic stem cell.

23. A method of making a transgenic non-human animal comprising the steps of:

(a) introducing into an embryo cell of said animal one or more of a nucleic acid vector according to any of claims 1 to 18;

(b) introducing the embryo from step (a) into a female animal;

(c) sustaining the female in step (b) until such time as the embryo has sufficiently developed and is borne from the female; and

(d) sustaining the transgenic animal.

24. A method according to claim 23 wherein said vector is introduced firstly into a non-human embryonic stem cell which is subsequently introduced into a blastocyst of said animal.

25. A method according to claim 24 wherein both of

the vectors encoding said human Tau and said protein capable of modulating human Tau according to claims 1 to 10 and 11 to 18 respectively are introduced into said stem cell.

26. A method according to any of claims 23 to 25 wherein said non-human animal is a mammal.

27. A method according to claim 26 wherein said mammal is a mouse.

28. A method according to claim 23 or 24, comprising the step of introducing a vector according to any of claims 1 to 10 into a first animal and a vector according to any of claims 11 to 18 into a second animal, crossing said first and second animals and selecting among the progeny those that express both said human Tau and said protein capable of modulating human Tau protein.

29. A method of making a transgenic non-human animal, which expresses a human Tau protein comprising the steps of:

(a) introducing sequentially or simultaneously into an embryo cell of said animal a first nucleic acid vector comprising a transgene capable of expressing said human Tau protein in the nervous system of said animal and a second nucleic acid vector comprising a sequence of nucleotides exhibiting a region of homology with a sequence encoding an equivalent Tau protein in said animal or with a region flanking or adjacent said sequence so as to facilitate integration of said vector into the genome of said animal by homologous recombination and which upon integration into the genome of said animal

is capable of preventing expression of endogenous Tau protein from said animal;

(b) introducing the embryo from step (a) into a female animal,

(c) sustaining the female in step (b) until such time as the embryo has sufficiently developed and is borne from the female; and

(d) sustaining the transgenic animal.

30. A method according to claim 29 wherein each of said first and second nucleic acid vectors are introduced in the same embryo cell.

31. A method according to claim 29 or 30 wherein said transgenic non-human animal is a mammal.

32. A method according to claim 31 wherein said mammal is a mouse.

33. A method of generating a transgenic non-human animal which is a model for Alzheimers disease or related neurodegenerative disorders, comprising the steps of crossing a first transgenic non-human animal comprising a vector according to any of claims 1 to 10 in its genome with a second transgenic non-human animal comprising a vector according to any of claims 11 to 18 in its genome, selecting among the progeny those that express both human Tau protein and said protein capable of modulating human Tau protein.

34. A method according to claim 33 wherein said nucleic acid vector in said first transgenic animal comprises a vector according to claim 9 or 10.

35. A method according to claim 34 wherein said second transgenic animal comprises a vector according to any of claims 11 to 18.

36. A method according to claim 34 which further comprises introducing into said second animal a vector comprising a transgene encoding Cre recombinase.

37. A transgenic non-human animal obtainable according to the methods of any of claims 23 to 36.

38. A transgenic knockin-knockout non-human animal that is a model for neurodegenerative disorders, comprising:

(a) an introduced DNA sequence encoding and capable of expressing heterologous Tau protein in the nervous system of the animal so as to prevent expression of the equivalent Tau protein in said animal or a related or equivalent protein in said animal in favour of said heterologous Tau protein; and

(b) a DNA sequence encoding and capable of expressing a protein capable directly or indirectly of modulating said heterologous Tau protein.

39. A transgenic non-human animal according to claim 38 wherein said sequence in step (a) comprises a vector according to any of claims 1 to 10.

40. A transgenic non-human animal according to claim 38 wherein said sequence according to step (b) comprises a vector according to any of claims 11 to 18.

41. A transgenic non-human animal according to claim 40 wherein said sequence according to step (b) is a kinase.

42. A method of identifying a compound which

modulates human kinase mediated phosphorylation of human Tau protein which method comprises administering a test compound to a non-human animal according to claim 41 expressing both said human Tau protein and said human kinase and monitoring the phosphorylation profile of said Tau protein compared to one of said transgenic animals which has not been administered with the compound.

43. A compound obtainable according to the method of claim 42.

44. A pharmaceutical composition comprising a compound according to claim 43 together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

45. Use of a compound according to claim 43 in the manufacture of a medicament for the treatment of neurodegenerative disorders.

46. Use according to claim 45, wherein said neurodegenerative disorders comprise any of FTDP-17 (Fronto-temporal dementia associated with Parkinson's disease), Cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy , Pick's disease, Dementia Pugilistica, Dementia with tangles only, dementia with tangles and calcification, Down syndrome, Myotonic dystrophy, Niemann Pick's disease type C, Parkinsonism-dementia complex of Guam, Postencephalic Parkinsonism, Prion diseases with tangles, subacute sclerosing panencephalitis.

47. A method of treating neurodegenerative disorders mediated by phosphorylation of human Tau protein comprising administering to a patient a compound as defined in claim 43 or a composition according to

claim 44.

48. A method of generating a transgenic non-human animal which is a model for Alzheimers disease or related neurodegenerative disorders, comprising the steps of crossing a first transgenic non-human animal comprising a vector having, i) a nucleic acid sequence encoding a human Tau protein, ii) a sequence capable of directing expression of said human Tau protein in the nervous system of said animal and iii) a targeting sequence which comprises a nucleotide sequence exhibiting a sufficient degree of homology with equivalent Tau protein in said animal or flanking sequences thereof, which facilitates integration of said vector into the genome of said animal by homologous recombination; with a second transgenic non-human animal comprising a vector according to claim 11, selecting among the progeny those that express both human Tau protein and said protein capable of modulating Tau protein.

49. A method according to claim 48 wherein said vector in said first and/or said second transgenic non-human animal comprises a stop sequence capable of preventing expression of said human Tau protein or said protein capable of modulating Tau protein which sequence is flanked by two loxP sites capable of undergoing reciprocal conservative DNA recombination with the resulting excision of said stop sequence.

50. A transgenic non-human animal obtainable according to the method of claim 48 or 49.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
BOULT WADE TENNANT
Attn. BALDOCK, Sharon Claire
Verulam Gardens
70 Gray's Inn Road
London WC1X 8BT
UNITED KINGDOM

Applicant's or agent's file reference SCB/52246002	Date of mailing *(day/month/year)* 04/09/2001
International application No. PCT/EP 00/06171	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant JANSSEN PHARMACEUTICA N.V.	International filing date *(day/month/year)* 30/06/2000

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of th International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Carla Louro

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application I English, the letter must be in English; if the language of the international application is French, th letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The lett r must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file referenc	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
SCB/52246002		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/06171	30/06/2000	02/07/1999
Applicant		
JANSSEN PHARMACEUTICA N.V.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   DOUBLE TRANSGENIC ANIMALS AS MODELS FOR NEURODEGENERATIVE DISEASE

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 14

   [ ] as suggested by th applicant.

   [X] because the applicant failed to suggest a figur .

   [ ] because this figure better characterizes th invention.

   [ ] None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation f item 5 of the first sheet)

There is provided transgenic animals comprising:1.a nucleic acid vector a) sequence encoding a human Tau protein; (b) a sequence capable of directing expression of said human Tau protein in the nervous system of a non-human animal; and (c) a targeting sequence which facilitates integration of said vector into the genome of said animal so as to prevent expression of equivalent Tau protein; a nucleic acid vector comprising: (a) a nucleic acid sequence encoding a human protein capable of modulating human Tau protein; (b) a sequence capable of directing expression of said protein in the nervous system of said animal; and (c) a targeting sequence capable of facilitating integration of said vector into the genome of said animal optionally at a position corresponding to a sequence in said animal encoding an equivalent of said human protein.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06171

A. CLASSIFICATION OF SUBJECT MATT
IPC 7 C12N15/00 A0[redacted]7/027 C07K14/47 C12N5/10 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 05466 A (INST OF PSYCHIATRY ;ANDERTON BRIAN HENRY (GB); MILLER CHRISTOPHER) 23 February 1995 (1995-02-23) page 4, line 1 - line 12 page 15, line 30 -page 16, line 6	40,43
Y	page 12, line 25; claims 12-15,20,30-38,45-49	1-51
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2001	04/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chambonnet, F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GUO Q, SEBASTIAN L, SOPHER BL, MILLER MW, WARE CB, MARTIN GM, MATTSON MP.: "Increased vulnerability of hippocampal neurons from presenilin-1 mutant knock-in mice to amyloid beta-peptide toxicity: central roles of superoxide production and caspase activation." JOURNAL OF NEUROCHEMISTRY, vol. 72, no. 3, March 1999 (1999-03), pages 1019-1029, XP001020319 page 1020, column 1, paragraph 3 -column 2, paragraph 3 ---	1-51
Y	MICHEL GOEDERT & MASATO HASEGAWA.: "The Tauopathies Toward an Experimental Animal Model" AMERICAN JOURNAL OF PATHOLOGY, vol. 154, no. 1, January 1999 (1999-01), pages 1-6, XP002923749 page 3, column 2, paragraph 2 ---	1-11, 30-33
Y	GÖTZ, J. ET AL.: "Somatodendritic localization and hyperphosphorylation of tau protein in transgenic mice expressing the longest human brain tau isoform" EMBO JOURNAL, vol. 14, no. 7, 3 April 1995 (1995-04-03) - 1304, page 1313 XP002175363 EYNSHAM, OXFORD GB cited in the application the whole document ---	1-9, 30-33
Y	BRION J-P ET AL: "TRANSGENIC EXPRESSION OF THE SHORTEST HUMAN TAU AFFECTS ITS COMPARTMENTALIZATION AND ITS PHOSPHORYLATION AS IN THE PRETANGLE STAGE OF ALZHEIMER'S DISEASE" AMERICAN JOURNAL OF PATHOLOGY, PHILADELPHIA, PA, US, vol. 154, no. 1, January 1999 (1999-01), pages 255-270, XP000965124 ISSN: 0002-9440 the whole document ---	1-6, 30-33
A	KÜHN ET AL: "Advances in gene targeting methods" CURRENT OPINION IN IMMUNOLOGY, CURRENT BIOLOGY LTD. LONDON, GB, vol. 9, 1997, pages 183-188, XP002133099 ISSN: 0952-7915 the whole document ---	1-40

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SAUER BRIAN: "Inducible gene targeting in mice using the Cre/lox system." METHODS, vol. 14, April 1998 (1998-04), pages 381-392, XP001019712 figures 2-4 ---	10,11,38
Y	BROWNLEES J ET AL: "TAU PHOSPHORYLATION IN TRANSGENIC MICE EXPRESSING GLYCOGEN SYNTHASE KINASE-3BETA TRANSGENES" NEUROREPORT,RAPID COMMUNICATIONS OF OXFORD, OXFORD,GB, vol. 8, no. 15, 20 October 1997 (1997-10-20), pages 3251-3255, XP000974561 ISSN: 0959-4965 cited in the application the whole document ---	12
Y	HARADA A. ET AL.: "Altered microtubule organization in small-calibre axons of mice lacking tau protein" NATURE., vol. 369, no. 6480, 9 June 1994 (1994-06-09), pages 488-491, XP002175364 MACMILLAN JOURNALS LTD. LONDON., GB ISSN: 0028-0836 the whole document ---	30-33
P,Y	SPITTAELS K ET AL: "PROMINENT AXONOPATHY IN THE BRAIN AND SPINAL CORD OF TRANSGENIC MICE OVEREXPRESSING FOUR-REPEAT HUMAN TAU PROTEIN" AMERICAN JOURNAL OF PATHOLOGY,PHILADELPHIA, PA,US, vol. 155, no. 6, December 1999 (1999-12), pages 2153-2165, XP000974569 ISSN: 0002-9440 the whole document ---	1-19
T	SPITTAELS K, ET AL.: "Glycogen synthase kinase-3beta phosphorylates protein tau and rescues the axonopathy in the central nervous system of human four-repeat tau transgenic mice" J BIOL CHEM. , vol. 275, no. 52, 29 December 2000 (2000-12-29), pages 41340-41349, XP002175365 the whole document ---	12

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International Application No
PCT/EP 00/06171

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	DAWSON, H.N. ET AL.: "Tau distribution in a human tau gene transgenic/mouse tau knock out model" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 25, no. 1-2, October 1999 (1999-10), page 790 XP001020341 abstract & 29th Annual Meeting of the Society for Neuroscience, Miami Beach, Florida, USA October 23-28 1999 ---	30
T	DAWSON, H.N. ETAL.: "Inhibition of neuronal maturation in primary hippocampal neurons from tau deficient mice" JOURNAL OF CELLULAR BIOLOGY, vol. 114, no. pt 6, March 2001 (2001-03), pages 1179-1187, XP001020383 the whole document -----	1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 44-48

Present claims 44 to 48 relate to a compound, a composition comprising it and methods using thereof, defined by reference to a desirable characteristic, namely being obtainable by a method of screening using a transgenic animal as described in claim 43.
The claims cover all compounds having this characteristic, all compositions comprising them and all methods using thereof, whereas the application provides no support within the meaning of Article 6 PCT and no disclosure within the meaning of Article 5 PCTs. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has not been carried out for those parts of the claims which appear to be not clear, not supported and disclosed.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/06171

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 48 is directed to a method of treatment of the human/animal body. Moreover the search could not been carried out and based on the alleged effects of the compound/composition claimed in claims 44 to 47 because no meaningful search was possible (cf supplement sheet) .

2. [X] Claims Nos.: 44-48
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/06171

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9505466 A	23-02-1995	EP 0716700 A	19-06-1996
		GB 2295395 A,B	29-05-1996
		US 5994084 A	30-11-1999